



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB91/01509 (22) International Filing Date: 5 September 1991 (05.09.91) (30) Priority data: 9019413.5 5 September 1990 (05.09.90) GB (71) Applicant (for all designated States except US): BEECHAM GROUP PLC [GB/GB]; Four New Horizons Court, Harlequin Avenue, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): GREENWAY, Michael, John [GB/GB]; SmithKline Beecham Pharmaceuticals, Clarendon Road, Worthing, West Sussex BN14 8QH (GB). BLOWER, Peter, Robin [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).		(74) Agents: RUSSELL, Brian, John et al.; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US. Published With international search report.
(54) Title: TOPICAL TREATMENT AND COMPOSITION (57) Abstract A pharmaceutical composition for topical application to a mammal comprising MNA, or a pharmaceutically acceptable salt thereof, and a topical pharmaceutically acceptable carrier.		

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Exhibit 7

FOR THE PURPOSES OF INFORMATION ONLY

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+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

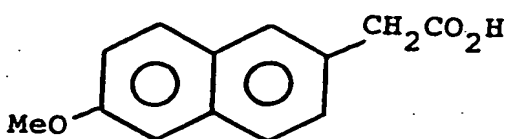
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TOPICAL TREATMENT AND COMPOSITION

This invention relates to the treatment of inflammation by topical administration and a pharmaceutical composition thereof, two novel salts of 6-methoxy-2-naphthylacetic acid and a process for making these salts.

6-Methoxy-2-naphthylacetic acid (MNA):

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(MNA)

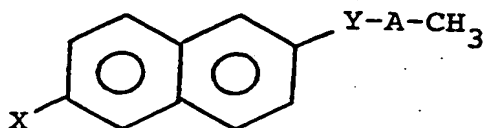
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is disclosed in Jones et al, J. Amer. Chem. Soc., 70, 2843 (1948) as an intermediate for preparing penicillins.

MNA is also mentioned in U.K. Patent Specification No. 20 1,211,134 (Syntex) wherein oral pharmaceutical compositions comprising MNA and a pharmaceutically acceptable carrier and its use in the treatment of inflammation are disclosed.

EP-A-0 167 062 discloses topically effective anti-inflammatory pharmaceutical compositions which comprise a compound of the formula (I):

30



(I)

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wherein X is a chlorine or bromine atom or a methoxyl, methylthio or alkyl group of 1-4 carbon atoms; Y is a -CHR₁-CH₂- or -CR₁=CH- group where R₁ is a hydrogen atom or a methyl group and A is a CHOH or CO group, and a
5 pharmaceutically acceptable topically effective carrier.

We have now found that 6-methoxy-2-naphthylacetic acid (MNA) or a pharmaceutically acceptable salt thereof unexpectedly possesses local topical anti-inflammatory activity, and
10 possesses systemic anti-inflammatory activity when administered topically.

Accordingly, the present invention provides a pharmaceutical composition for topical application to a mammal comprising
15 MNA, or a pharmaceutically acceptable salt thereof, and a topical pharmaceutically acceptable carrier.

The present invention further provides a topical pharmaceutical composition for use in the treatment and/or
20 prophylaxis of inflammation which comprises MNA, or a pharmaceutically acceptable salt thereof and a topical pharmaceutically acceptable carrier.

The present invention also provides the use of MNA or a
25 pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prophylaxis of inflammation by topical administration to mammals, including humans.

30 The present invention also provides a method of treatment or prophylaxis of inflammation in mammals, including humans, comprising topical administration of an anti-inflammatory topically effective amount of MNA or a pharmaceutically acceptable salt thereof.

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MNA may also form solvates such as hydrates, and the invention also extends to these forms. When referred to

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herein, it is understood that the term 'MNA' also includes solvates thereof.

MNA can also form salts with bases, such as conventional
5 pharmaceutically acceptable bases.

The present invention provides the following novel salts of MNA i.e. 6-methoxy-2-naphthylacetic acid sodium salt and 6-methoxy-2-naphthylacetic acid potassium salt.

10

The present invention also provides a process for the preparation of the sodium or potassium salt which comprises forming a solution of the sodium or potassium salt of MNA respectively and precipitating or isolating the product from
15 solution.

The solution of the abovementioned salts may be formed by dissolving the free acid of MNA in an organic solvent and adding sodium ethylhexanoate or potassium ethylhexanoate,
20 respectively.

Alternatively, the abovementioned salts may be formed by dissolving the free acid of MNA in a water immiscible organic solvent and extracting the MNA as the sodium or potassium
25 salt by extracting into an aqueous solution containing sodium hydroxide or potassium hydroxide respectively. The appropriate salt may then be isolated by precipitation with an appropriate water miscible solvent, such as acetone, or the aqueous solution of the salt may be freeze-dried.

30

MNA or pharmaceutically acceptable salts thereof, may be used in the topical treatment of atopic and contact dermatitis, psoriasis, eczema and other inflammatory dermatoses and in inflammatory conditions of eyes, ears,
35 nose and throat.

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MNA or pharmaceutically acceptable salts thereof, may also be used in the treatment by topical administration of osteo- and rheumatoid arthritis and sprains, strains, tendinitis and bursitis.

5

The amount of MNA or pharmaceutically acceptable salts thereof, present in the formulation should be at least sufficient to maintain an effective concentration at the site of action between applications without showing signs of
10 toxicity. It will be appreciated that the topically effective amount of MNA or a pharmaceutically acceptable salt thereof, will depend on a number of factors such as the nature and severity of the disorder being treated. The optimum concentration of MNA or a pharmaceutically
15 acceptable salt thereof, will depend on its solubility in the formulation and should be at a level exceeding its solubility in order to provide a reservoir and to maintain it at a saturated concentration within the vehicle. A typical formulation suitable for treating an adult human
20 will suitably contain 0.1 to 10% by weight more suitably 0.1 to 3% by weight of MNA or a pharmaceutically acceptable salt thereof.

A topical pharmaceutical composition for the method of
25 treatment of the present invention may be administered from 1 to 6 times daily, and more usually from 2 to 4 times daily.

The compositions of the present invention may be made up in
30 any conventional carriers suitable for the topical administration of anti-inflammatories, for example ointments, creams, lotions, gels, liniments, sprays, gel sticks, patches, films, dressings and aerosols. These are formulated as known in the art, for example as described in
35 standard text books of pharmaceuticals and cosmetics, such as Harry's Cosmeticology published by Leonard Hill Books, The British Pharmacopoeia and United States Pharmacopoeia/

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National Formulary. The compositions may also contain conventional additives such as preservatives and solvents to improve the drug's solubility, and penetration enhancers.

5 A suitable ointment base may conveniently comprise from 65 to 100% (preferably 75 to 96%) of white soft paraffin, from 0 to 15% of liquid paraffin, and from 0 to 7% (preferably 3 to 7%) of lanolin or a derivative or synthetic equivalent thereof.

10

The term 'soft paraffin' as used above encompasses the cream or ointment bases white soft paraffin and yellow soft paraffin. The term 'lanolin' encompasses native wool fat and purified wool fat. Derivatives of lanolin include in 15 particular lanolins which have been chemically modified in order to alter their physical or chemical properties and synthetic equivalents of lanolin include in particular synthetic or semisynthetic compounds and mixtures which are known and used in the pharmaceutical and cosmetic arts as 20 alternatives to lanolin and may, for example, be referred to as 'lanolin substitutes'.

One suitable synthetic equivalent of lanolin that may be used is the material available under the trade mark 25 'Softisan' known as 'Softisan 649'. Softisan 649, available from Dynamit Nobel Aktiengesellschaft, is a glycerine ester of natural vegetable fatty acids, of isostearic acid and of adipic acid; its properties are discussed by H. Hermsdorf in Fette, Seifen, Anstrichmittel, Issue No. 84, No.3 30 (1982), p.p. 3-6.

Another suitable ointment base may conveniently comprise a polyethylene - liquid paraffin matrix, for example that available from Squibb under the trade mark 'Plastibase'.

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A suitable cream base may conveniently comprise an emulsion system, in which two immiscible phases, an aqueous or polar

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phase and a lipid or oil phase are stabilised by an emulsifying agent(s) (emulsifier).

The oil phase of the emulsion may be constituted from known ingredients in a known manner. Whilst the phase may comprise merely an emulsifier (otherwise known as an emulgent), it is desirably comprised of a mixture of at least one emulsifier with one or more excipients including oils, fats and/or waxes, together with optional film formers and stabilisers as well as thickening and bodying agents.

Preferably, as explained in more detail below, an additional hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) make up the so called emulsifying wax, and the wax together with the oil and/or fat make up the so called emulsifying ointment base which forms the oil dispersed phase of the emulsions.

20

Topical emulsion formulations may be formulated in a number of ways, all of which depend primarily on the alignment of the emulgent or emulsifying agent and emulsion stabiliser at the oil/water interface, with the non-polar or lipophilic groups soluble in the oil phase and the polar or hydrophilic or lipophobic groups in the aqueous or continuous phase.

Thus the more polar hydrophilic emulgents result in oil-in-water emulsions. This principle has been systemised in the idea of a 'hydrophilic-lipophilic balance' (H.L.B). Griffen, W. C. J. Soc. Cosmet. Chem., 1954, 5, 249 and the various emulgents have been allocated H.L.B. numbers from which their behaviour with constituents of the aqueous and oil phases (to which are applied theoretical required H.L.B. figures) may be predicted.

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Emulgents and emulsion stabilisers suitable for use in the formulation of the present invention include polyoxyethylene sorbitan monostearate (polysorbate 60), sorbitan monostearate, sorbitan monooleate, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Lipophilic substances with relatively high melting points, such as beeswax, partial glycerides of capric and caprylic acids, or silicone oil, white soft paraffin or other mineral or vegetable oils are suitable. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol, diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a mixed ester of 2-ethyl hexanoic acid with a blend of cetyl or stearyl alcohols known as Crodamol CAP may also be used.

An example of a suitable emulsified system is as follows:-
From 5 to 15% cetostearyl alcohol, from 2 to 10% liquid paraffin, from 10 to 20% white soft paraffin, 0.5 to 2.0% carbomer 940, 0.5 to 1.5% sodium lauryl sulphate, 0 to 50% propylene glycol and from 10 to 65% water.

A suitable gel base may conveniently comprise a semi-solid system in which a liquid phase is constrained within a three dimensional polymeric matrix with a high degree of cross-linking. The liquid phase may conveniently comprise water, together with from 0 to 50% of water-miscible additives, for example glycerol, polyethylene glycol,

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ethoxydiglycol, ethanol or propylene glycol, and from 0.1 to 10%, preferably from 0.5 to 2%, of a thickening agent, which may be a natural product, for example tragacanth, pectin, carrageen, agar and alginic acid, or a synthetic or
5 semi-synthetic compound, for example methylcellulose and carboxypolymethylene ('carbopol'); together with one or more preservatives, if required, for example from 0.1 to 2% of methyl 4-hydroxybenzoate ('methyl parabenz') or
phenoxyethanol, together with a penetration enhancer such as
10 decylmethyl sulphoxide.

It should also be appreciated that the supersaturation technology mentioned in EP-A-0151953 and EP-A-0272045 may be utilized for preparing topical formulations of MNA or
15 pharmaceutically acceptable salts thereof, and this forms a further aspect of the present invention.

The other substances mentioned hereinabove as constituents of suitable ointment or cream bases and their properties are
20 discussed in standard reference works, for example pharmacopoeia (hereinabove).

The compositions of the invention may be produced by conventional pharmaceutical techniques. With MNA, or a
25 pharmaceutically acceptable salt thereof, being added at an appropriate point and ensured that it is well dispersed throughout the formulation.

If necessary the composition may be milled at any suitable
30 stage of the process.

A suitable sterilisation procedure may also be included if necessary. Alternatively raw materials are obtained in sterile condition and the compositions are produced
35 aseptically.

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The compositions of this invention may further contain other therapeutic agents such as anti-infective agents and/or anti-viral agents. Suitable anti-infective agents include the topically applicable antibacterial, anti-yeast and
5 anti-fungal agents already in use in topical anti-inflammatory preparations. As anti-viral agents, there may be particularly mentioned anti-herpes agents.

6-Methoxy-2-naphthylacetic acid (MNA) may be prepared as
10 described in U.K. Patent No. 1,211,134. (Example 1, pages 14 to 15).

The following examples illustrate the topical compositions of the present invention and the pharmacological test
15 illustrates effectiveness of the present invention.

Example 1 (cream)

The following ingredients are mixed together in a
20 conventional manner to form a topically effective pharmaceutical composition.

Cetostearyl Alcohol	7.33%
White soft paraffin	14.11%
25 Liquid paraffin	5.64%
Carbomer 940	1.00%
Sodium lauryl sulphate	0.85%
Propylene glycol	40.00%
MNA	3.00%
30 Water to	100.00%

Example 2 (Gel)

The following ingredients are mixed together in a
35 conventional manner to form a topically effective pharmaceutical composition.

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MNA	3.00%
Carbomer 940	1.00%
Propylene glycol	40.00%
Water to	100.00%

5

Example 3

The following ingredients were mixed together in a conventional manner to form a topically effective pharmaceutical composition.

MNA	0.2%
Ethoxydiglycol	40.0%
Hydroxyethyl cellulose	1.3%
15 Water to	100.0%

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Pharmacological Data1. Method (THF/Methanol as vehicle)

5 An acute inflammatory response was induced in the right hind paw of male Wistar rats (Bantin and Kingman, 190-260 gms, n=6 or 8) by sub-plantar injection with 0.1 ml of 1% carrageenan (Viscarin 109) in 0.9% sterile saline.

10 MNA was administered topically, to the previously shaven flank, two hours prior to carrageenan injection. The drug vehicle, tetrahydrofuran (THF): methanol (50:50), was applied to the shaven flank (200 µl) of control animals.

15 The area (4 cm²) of the flank of the rats was shaven and depilated (Immac) 24 hours prior to drug application.

Paw volume was quantified using a mercury plethysmograph 3 hours after carrageenan injection. Paw oedema was taken as
20 the difference in volume of the injected and non-injected paws.

Results

25	% MNA (w/v)	Topical Application to flank (200µl) % inhibition of control oedema
30	10	48.9* (p<0.001)

Vehicle = Tetrahydrofuran (THF): Methanol (50:50).

* Statistically Significant.

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2. Method (Gel base as vehicle)

An acute inflammatory response was induced in the right hind paw of male Wistar rats (OLAC, 160-2650 gms, n=6) by sub-plantar injection with 0.1 ml of 1% carrageenan (Viscarin 109) in 0.9% sterile saline.

Gel base drug formulations were administered topically to the previously shaven flank (nape of neck), 2 hours prior to carrageenan injection. The gels were applied to the skin (200µl) via a syringe and spread over the shaven area using a rubber-tipped applicator.

The rats were shaven to expose an area (4cm²) of skin at the nape of the neck 24 hours prior to drug application. All animals were housed individually throughout the experiment.

Paw volume was quantified using a mercury plethysmograph 3 hours after induction of carrageenan oedema. Paw oedema was taken as the difference in volume of the injected and non-injected paws.

Topical formulations of 6MNA: Anti-inflammatory activity che
carrageenan-induced rat paw oedema model

25

<u>Formulation:</u>	Gel base 1.	Propylene glycol (42.1%)
		Absolute alcohol (26.3%)
		Water (31.6%)
	Gel base 2.	Gel base 1 (97.5%)
		Decylmethyl sulphoxide (2.5%)
	Gel base 3.	Transcutol (40%)
		Water (60%)

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Gel base	% Inhibition paw oedema (mean +/- sem)
1	29.32 ± 7.22* (2.50%)
2	45.65 ± 6.62** 27.69 ± 9.09* (2.50%)
3	35.87 ± 5.39** (1.50%)

15

n=6/group, 200µl drug formulation applied to shaven flank
(nape of neck).

Values in parenthesis are actual drug concentrations (%)
20 supplied in each gel base formulation.

Statistically * p = < 0.05
Significant ** p = < 0.01

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Claims

1. A pharmaceutical composition for topical application to a mammal comprising MNA, or a pharmaceutically acceptable salt thereof, and a topical pharmaceutically acceptable carrier.
2. The use of MNA or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prophylaxis of inflammation by topical administration to mammals, including humans.
3. The use of MNA or a pharmaceutically acceptable salt thereof according to claim 2, for the manufacture of a medicament for the treatment or prophylaxis of osteoarthritis.
4. The use of MNA or a pharmaceutically acceptable salt thereof according to claim 2, for the manufacture of a medicament for the treatment or prophylaxis of rheumatoid arthritis.
5. The use of MNA or a pharmaceutically acceptable salt thereof according to claim 2, for the manufacture of a medicament for the treatment or prophylaxis of sprains and/or strains and/or tendinitis and/or bursitis.
6. A pharmaceutical composition for topical application, according to claim 1, which is in the form of a cream, lotion, liniment, spray, gel stick, patch film, dressing or aerosol.
7. A pharmaceutical composition for topical application according to claim 1 which is in the form of a gel.
8. A pharmaceutical composition for topical application according to claim 7 in which the gel comprises MNA,

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ethoxydiglycol, hydroxyethyl cellulose and water.

9. A pharmaceutical composition for topical application according to any one of claims 1, 6, 7 or 8 which contains 5 from 0.1 to 3% by weight of MNA.

10. 6-Methoxy-2-naphthylacetic acid sodium salt.

11. 6-Methoxy-2-naphthylacetic acid potassium salt.

10

12. A process for the preparation of 6-methoxy-2-naphthylacetic acid sodium salt which comprises forming a solution of the sodium salt of 6-methoxy-2-naphthylacetic acid and precipitating or isolating the product from 15 solution.

13. A process for the preparation of 6-methoxy-2-naphthylacetic acid potassium salt which comprises forming a solution of the potassium salt of 6-methoxy-2-naphthylacetic 20 acid and precipitating or isolating the product from solution.

14. A method of treatment and/or prophylaxis of inflammation in mammals comprising topical administration of 25 an anti-inflammatory topically effective amount of MNA or a pharmaceutically acceptable salt thereof.

15. A method of treatment and/or prophylaxis of osteoarthritis in mammals comprising topical administration 30 of an effective amount of MNA or a pharmaceutically acceptable salt thereof.

16. A method of treatment and/or prophylaxis of rheumatoid arthritis in mammals comprising topical administration of an

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effective amount of MNA or a pharmaceutically acceptable salt thereof.

17. A method of treatment and/or prophylaxis of sprains and/or strains and/or tendinitis and/or bursitis in mammals comprising topical administration of an effective amount of MNA or a pharmaceutically acceptable salt thereof.

18. A topical pharmaceutical composition according to claim 1 for use in the treatment and/or prophylaxis of inflammation, which comprises MNA, or a pharmaceutically acceptable salt thereof, and a topical pharmaceutically acceptable carrier.

19. A topical pharmaceutical composition according to claim 1 for use in the treatment and/or prophylaxis of osteoarthritis, which comprises MNA, or a pharmaceutically acceptable salt thereof and a topical pharmaceutically acceptable carrier.

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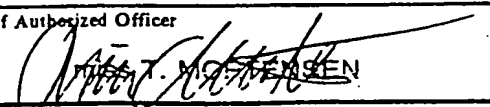
20. A topical pharmaceutical composition according to claim 1 for use in the treatment and/or prophylaxis of rheumatoid arthritis, which comprises MNA, or a pharmaceutically acceptable salt thereof and a topical pharmaceutically acceptable carrier.

21. A topical pharmaceutical composition according to claim 1 for use in the treatment and/or prophylaxis of sprains and/or strains and/or tendinitis and/or bursitis, which comprises MNA, or a pharmaceutically acceptable salt thereof and a topical pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 91/01509

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5 A 61 K 31/19 C 07 C 59/64		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.C1.5	A 61 K C 07 C	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ^o	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	EP,A,0167062 (BEECHAM GROUP PLC) 8 January 1986, see pages 1-2 (cited in the application) ---	1-9,14-21
Y	Eur. J. Clin. Pharmacol., volume 36, no. 3, 1989, Springer Verlag, M.J. Kendall et al.: "A pharmacokinetic study of the active metabolite of nabumetone in young healthy subjects and older arthritis patients", pages 299-305, see page 299 ---	1-9,14-21
A	US,A,4001301 (FRIED et al.) 4 January 1977 ---	
A	US,A,3873718 (HENZL et al.) 25 March 1975 -----	
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>^o Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
30-10-1991	13. 12. 91	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE		

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers
Authority, namely: because they relate to subject matter not required to be searched by this
Remark: Although claims 14-17 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9101509

SA 51124

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/12/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
EP-A- 0167062	08-01-86	AU-B-	584340	25-05-89
		AU-A-	4413285	20-02-86
		CA-A-	1246458	13-12-88
		JP-A-	61018718	27-01-86
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		US-A-	4097674	27-06-78
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